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blood and urine. Unfortunately, body fluid levels of cotinine in nonsmokers have never been correlated precisely with ambient nicotine exposures, as Repace and Lowrey assume, and body fluid levels in nonsmokers are affected by ingestion of nicotine from the ordinary diet.

- The level of "obvious risk" generated for cotinine by the Repace-Lowrey model could be achieved through the ingestion of common foods alone, in the absence of ETS exposure.

- Cotinine is a biologically inactive and non-carcinogenic substance metabolized from many common foods. Is the Repace-Lowrey estimate of "excess risk" based on this substance meaningful?

DRAFT 6

A CRITIQUE OF:

"AN ENFORCEABLE INDOOR AIR QUALITY STANDARD

FOR ENVIRONMENTAL TOBACCO SMOKE IN THE WORKPLACE,"

BY JAMES L. REPACE AND ALFRED H. LOWREY,

Risk Analysis, 13(4):463-474, 1993

Summary:

In their paper, Repace and Lowrey claim to have developed "a model which permits using atmospheric nicotine measurements to estimate nonsmokers' ETS lung cancer risks in individual workplaces for the first time." The model is a modification and extension of previous exposure and risk models developed by the authors.[1-2] Both models were heavily criticized in the scientific literature.[3-12]

The report presents no new data on workplace exposures to ETS, and the model developed to assess exposure and risk does not utilize available epidemiologic data or actual exposure data from the published literature. The available epidemiologic data on the workplace provide virtually no support to the claim that ETS exposures are associated with an increased risk of lung cancer for nonsmokers. Moreover, actual measurements of constituents of ETS in the air of offices, restaurants and public places are five to ten times lower than the exposure estimates generated by Repace and Lowrey's theoretical model.

The estimates for "acceptable" and "obvious" risks proposed by the authors are based upon erroneous exposure estimates

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for ETS-related respirable suspended particulate (RSP) (smoke particles), nicotine and cotinine, a substance converted from nicotine by the body. The calculated "acceptable risk" for airborne RSP attributable to ETS is 1,000 times lower than the permissible exposure levels set by the World Health Organization, the U.S. EPA and Health and Welfare, Canada; the calculated "acceptable risk" level is also well below background levels reported for RSP in smoke-free environments. The suggested permissible airborne exposure level for nicotine is so minuscule that it is below detection limits for sophisticated air monitoring devices, and the level of "obvious risk" calculated for cotinine levels in the body fluids of nonsmokers is attainable by the ingestion of common foods -- potatoes, tomatoes, eggplant and fruits --in the absence of any exposure to ETS.

Background

A model that generates "acceptable" levels of exposure for various ETS constituents that are lower than the detection limits of sophisticated air monitoring devices, or one that provides estimates of "obvious risk" that are surpassed in individuals who are not even exposed to ETS, must be seriously questioned. The model's principal shortcoming is found in the estimates generated for nonsmoker exposure to various ETS constituents in the workplace. The model-generated estimates of exposure do not track

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reality and are not remotely similar to the available empirical data regarding actual workplace exposure to ETS constituents.

In 1980, Repace and Lowrey published a description of a model for predicting and estimating ETS exposures based on the use of respirable suspended particulate (RSP) as a marker for ETS.[1] The authors also sampled the air of meeting and game rooms, bars, sandwich shops and similar venues for RSP. They claimed that the average level of RSP measured in the various locations verified their predictive model (approximately 250 micrograms per cubic meter of air (ug/m^3)).[1,2]

The sampling procedures used by the authors were challenged, as was their assumption that all RSP in the air is attributable to ETS.[3-6] Dust indoors contributes substantially to RSP. Chemical analyses have been developed for estimating the relative contribution of ETS to total RSP indoors. Field studies indicate that ETS-RSP comprises from 10% to 50% of total indoor air RSP, and typically contributes 25 to 35% of the RSP present in an environment in which smoking takes place.[13]

Actual measurements of RSP in hundreds of offices and similar workplaces reveal that source-apportioned RSP due to ETS is typically 5 to 10 times lower than the "average" level reported by Repace and Lowrey.[14-19]

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- One recent investigation reported that average levels of RSP in 330 offices in which smoking was permitted was 46 micrograms per cubic meter (ug/m^3), compared with an average of 20 ug/m^3 reported for 254 nonsmoking offices;[19]

- Four studies on the measurement of RSP from ETS in the workplace were reviewed by scientists from Oak Ridge National Laboratories (ORNL) in their 1992 monograph on the chemistry and measurement of ETS.[13] The four studies reported average RSP concentrations from ETS of: 27 ug/m^3 for 131 offices; 32 ug/m^3 for 22 offices; 28 ug/m^3 for 194 offices and 44 ug/m^3 for 31 offices;

- Authors of a 1988 survey of 31 offices in Ottawa, Canada, cited by Repace and Lowrey (Reference No. 70), noted that: "based on the results of this survey, the average office worker was exposed to 0.0039 cigarette equivalent per hour (using nicotine as a marker), 0.0010 cigarette equivalent per hour [for ETS-related RSP]. . . the time for exposure to 1 cigarette equivalent would have been 260 hours

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(using nicotine) or 1,000 hours [for ETS-related RSP]."[14]

The overestimation of RSP attributable to ETS by the authors' 1980 exposure model was applied to their risk assessment model published in 1985.[2] In their 1985 paper, the 250 ug/m^3 "average" exposure of RSP estimated by the authors' 1980 exposure model generates an estimated average daily "lung exposure" (dose) of 1430 ug RSP. (The "dose" function is calculated by the equation: exposure (250 ug/m^3) (x) duration (8 hours) (x) rate of respiration (1 m^3/hour).*

- The risk model was criticized because its assumptions for exposure and dose were not based on actual measurements. One commenter observed that actual exposure measurements reported by other researchers ranged from "10-to-100-fold less than that in the Repace and Lowrey model;"[9]

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* By comparing the rate of lung cancer reported in a single study on Seventh Day Adventists (presumed to be unexposed to ETS) with that reported for a population of non-Seventh Day Adventists (who presumably were exposed to ETS), the authors report a mortality rate for non-Seventh Day Adventists that is 2.4 times that of the Seventh Day Adventist group. Extrapolated to the general population of an estimated 63 million nonsmokers in the U.S., the mortality rate generates an estimate of 4,700 lung cancer deaths per year. This is an excess mortality rate of 7.4 lung cancer deaths per 100,000, or 5 lung cancer deaths per 1 milligram (1000 ug) of RSP per day (derived by dividing 7.4 lung cancer deaths by 1.43 mg (1430 ug) of daily RSP "lung exposure.")

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- Other scientists suggested that the author's model used erroneous and "unrealistic assumptions" that resulted in overestimations of risk and exposure.[7,8,10-12] In particular, one analysis demonstrated that, depending upon which assumptions were selected, model-generated estimates of exposure and risk could vary as much as 300-fold;[8]

- The estimated "lung exposure" of ETS-related RSP generated by the Repace-Lowrey model does not resemble other estimates published in the scientific literature.[8,20-24] This is because the Repace-Lowrey model employs unrealistically high levels of average exposures to RSP, and because the model fails to factor in important variables such as particle behavior and deposition, lung retention and clearance mechanisms;[20]

- Based upon the above-mentioned factors and upon realistic exposure measurements, several authors have independently estimated levels of ETS-RSP uptake by nonsmokers to approximate 0.02% (1/200 of one percent) that of the particulate uptake for an active smoker;[8,21-23]

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- Other scientists report that "the lung cell doses for average ETS-exposed nonsmokers are probably between 1/10,000 and 1/100,000 of equivalent cell doses for average mainstream active smokers. In practical terms, this implies an annual retained dose of tobacco smoke components equivalent to far less than the dose from the active smoking of one cigarette somehow evenly dispersed over one year period." [emphasis added];[20]

- Another researcher recently reviewed the available published data on exposure to ETS constituents, including RSP from ETS.[24] Based upon actual levels of RSP averaged over a number of studies in the workplace environment, the researcher calculated a "retained dose" for a nonsmoker that approximated 2/5 to 1/2 of a single cigarette (equivalent) over a year of exposure to ETS. [emphasis added) He remarked: "Toxicologically, it does not make any sense that retained doses of these very small amounts of respirable particulate from ETS would result in disease."

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The Repace-Lowrey Nicotine Model

The model described in Repace and Lowrey's recent paper converts the authors' previous models based on estimated exposures to RSP into a single model for estimating risk and exposure that is based upon nicotine (and its metabolite, cotinine). This exercise was undertaken because, according to Repace and Lowrey, "an indoor air quality standard based upon RSP. . . would be difficult to enforce." (p. 464) RSP, the authors now apparently realize, "is not unique to ETS." (p. 464) The authors also argue that "quantification of ETS exposure and risk for regulatory purposes must be predicated upon substances uniquely associated with tobacco combustion, such as nicotine in workplace air." The authors believe that nicotine, and its metabolite, cotinine, "are the best available markers for ETS exposure and dose," and "therefore also serve as the most suitable markers for the carcinogenic effect of ETS," even though the authors concede nicotine and cotinine's "apparent lack of carcinogenic activity." (p. 464)

The first step in Repace and Lowrey's attempt to convert the RSP-based exposure model to one based upon nicotine requires the assumption that there is a constant ratio between airborne RSP and airborne nicotine. A constant ratio would make extrapolation from one model to another possible. Repace and Lowrey suggest a

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constant ratio of 10:1 for RSP and nicotine. Contrary to Repace and Lowrey, the existence of such a ratio is an open question according to the scientific literature.[25] However, of critical importance is Repace and Lowrey's estimate for exposure to nicotine. The estimate is derived by dividing the "lung exposure" estimate of 1430 ug/day RSP by 10 (the 10:1 ratio) to yield an estimated "lung exposure" of 143 ug/day nicotine. Unfortunately, the authors do not appear aware of the fact that nicotine appears in the gas-phase of ETS and therefore would exhibit kinetic and depositional properties that are different from RSP (particle-phase substances). Moreover, the "lung exposure" estimate of 143 ug/day for nicotine represents a gross over-estimation when compared to actual nicotine measurements in the workplace reported in the scientific literature. For example:

- In the Canadian workplace study cited by Repace and Lowrey (Reference No. 70), the researchers measured nicotine in the air of offices and restaurants in Ottawa, Canada.[14] They reported average nicotine exposure levels equivalent to 3/100 of a cigarette per 8 hour workday in an office, and to 3/1000 cigarette exposure during a 1 hour meal in a restaurant;

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- In a study of over 3,000 travel, work, home and leisure locations in the U.K., investigators reported nicotine levels that were below detection limits for 3/4 of all sites, even though smoking was known to have occurred in nearly half of those locations;[26]

- In another study cited by Repace and Lowrey (Reference No. 71), average nicotine levels reported for 156 office samples and 170 restaurant samples were 4.8 and 5.1 ug/m^3, respectively.[15] According to the study's authors, "estimated mean exposure for an 8-hour workday in an office is 0.02 cigarette equivalent and for a 1-h meal in a restaurant, 0.003 cigarette equivalent;"

- In a recent study of 585 offices, researchers reported nicotine levels between zero and 2.5 ug/m^3 in nearly all of the nonsmoking offices sampled. Nicotine levels averaged .02 ug/m^3 for all nonsmoking offices, and 6.7 ug/m^3 for smoking offices;[19]

- Canadian researchers reported nicotine levels of 1 ug/m^3 or less in nonsmoking offices that received recirculated air from designated smoking areas.[27] This is an exposure equivalent for nicotine of a

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little more than 1/1000 of a single cigarette. Using Repace and Lowrey's over-simplified model for the determination of "lung exposure" to nicotine, it would take about 3 hours for a nonsmoker to "absorb" 1 ug of nicotine. Expressed another way, it would take over 400 continual hours of such exposure -- 10 weeks of work -- to be exposed to the level generated by the Repace and Lowrey model for a single day of exposure to nicotine (143 ug)!

The Repace-Lowrey Cotinine Model

In the next step of their analysis, Repace and Lowrey attempt to verify the nicotine "exposure" model by comparing estimates of exposure to reported levels of cotinine in body fluids of nonsmokers. An estimative model for cotinine is developed by the authors, and the predictions generated by the model for cotinine are compared with levels of cotinine actually measured in several studies of nonsmokers.

Although Repace and Lowrey suggest that their model predictions for cotinine levels correlate with, and therefore support, the predictions of their nicotine "exposure" model, the exercise by the authors is not meaningful. That is because the so-called correlation between model-generated estimates for nicotine

in the air and cotinine levels in body fluids has no basis in reality -- the results for nicotine are not based upon actual ambient measurements.

A more fundamental flaw in Repace and Lowrey's analysis of cotinine follows from the authors' assumptions that: (1) cotinine is a reliable quantitative measure of ETS exposure; (2) airborne levels of nicotine can be correlated with body fluid levels of cotinine, and (3) body fluid levels of cotinine are determined solely by airborne levels of nicotine. None of these assumptions has been borne out in the scientific literature.

- Cotinine has never been demonstrated to be a reliable quantitative marker for ETS (or nicotine) exposure in nonsmokers. According to one of the reviewers of the present Repace-Lowrey study, (also cited in their paper (Reference No. 28)): "Within a given exposure level there was considerable variability in cotinine values. Cotinine was chosen as a biological marker of ETS exposure because it is specific to tobacco smoke. However, cotinine levels in body fluids may not only reflect environmental exposure to tobacco smoke, but also factors that influence uptake and metabolism of nicotine."[28] The authors conclude:

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The relatively modest correlation between reported ETS exposure and urinary cotinine indicated that other factors such as differing metabolic rates and body size may have a confounding effect on the relationship between cotinine levels and questionnaire measures of ETS exposure. In view of this finding, we would recommend against using cotinine levels as a strictly quantitative indicator of ETS.

A concentration of cotinine at any given time depends not only upon the exposure and dose of nicotine, but also upon the rate of metabolic conversion of nicotine to cotinine in an individual, as well as upon the rate of elimination or clearance of cotinine from the body. Individuals metabolize nicotine in different ways at different times, and elimination and clearance rates for cotinine vary among individuals. Any single determination of a given cotinine level in the body fluid of an individual is therefore subject to physiological, pathological and genetic variabilities.[29-35] It is thus impossible to extrapolate, with any degree of confidence or reliability, from cotinine concentrations to nicotine exposure in the ambient air, given inter-individual variations in the metabolism and clearance of cotinine.

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Can ambient levels of nicotine be correlated with body fluid levels of cotinine, as assumed by Repace and Lowrey? According to researchers cited by Repace and Lowrey themselves, the answer is no. For example, Curvall and colleagues (Reference No. 46, Repace and Lowrey) note in another study: "The pharmacokinetics of nicotine and cotinine have been evaluated in smokers and nonsmokers at concentrations usually achieved by smokers, and little is known about the kinetics of these compounds at concentrations found in nonsmokers exposed to environmental tobacco smoke nicotine. . . the suitability of cotinine as a marker of environmental tobacco smoke nicotine exposure has only been evaluated in field studies; no data are available on the relationship between low dose nicotine intake and cotinine concentrations in nonsmokers."[29]

In a series of studies by other authors cited by Repace and Lowrey (Reference No. 67), Coultas et al., compared ETS exposure measurements, questionnaire estimates of exposure and cotinine levels in nonsmokers.[36-38] They report:

> During one workshift, we obtained questionnaires on exposure, saliva and

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> urine for cotinine, and personal air samples for respirable particles and nicotine. The levels of cotinine, respirable particles, and nicotine varied widely with self-reports of exposure to ETS . . . .

- Idle of the United Kingdom wrote in 1989:[30]

> The complex of dynamic interactions which leads to a certain salivary or urinary concentration of cotinine at one point in time following exposure to a defined amount of airborne nicotine needs to be dissected. . . single point cotinine concentrations can give no more than a clue to a past exposure to pyridine alkaloids of unknown amount, at an unspecified time, by an unknown route of entry and from unknown origins.

- The assumption that cotinine levels in body fluids are the sole result of airborne nicotine exposures from ETS is undermined by a third area of research that has identified significant sources of nicotine in the common diet. According to a recent report by Domino, et al., trace levels of nicotine can be found in a number of human foods such as potatoes, tomatoes and eggplant.[39] The researchers report that their findings independently verify previous reports by other investigators.[40-42] Recorded levels of nicotine in various vegetables such as cauliflower, eggplant, potatoes and tomatoes range from about 3

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nanograms/gram to about 100 nanograms/gram -- where a nanogram is 1 billionth of a gram and 28 grams are equivalent to one ounce. If one assumes complete absorption of the nicotine from vegetables during ingestion, an individual would consume about 10 grams of eggplant, 65 grams of potatoes or 93 grams of tomatoes to obtain a 1 microgram dosage of nicotine. This translates into about 1/3 ounce of eggplant, 5 ounces of potato, or about 8¼ ounces of ripe tomato to account for a 1 ug intake of nicotine. (A nonsmoker exposed to 1 ug/m^3 of nicotine in the air would take approximately 3 hours to "absorb" 1 ug.)

Similarly, Davis, et al. (1991) calculated a total of 8.8 ug intake of nicotine per day from the consumption of average quantities of the foods mentioned above.[42] This would result in a urinary cotinine concentration estimated at approximately 0.6 ng/ml. Maximum consumption of nicotine-containing foods could result in an estimated urinary cotinine concentration of 6.2 ng/ml. This range of values for cotinine due to diet is comparable to levels reported in various studies for nonsmokers who are exposed to ETS.

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Thus, cotinine is not a reliable quantitative measure of ETS exposure. This is because body fluid levels of cotinine cannot be attributed solely to nicotine in ETS, and because body fluid levels of cotinine do not correlate well with actual ambient air exposures to nicotine or with other ETS constituents.

Risk Estimates

Repace and Lowrey apply the exposure estimates generated by their particulate, nicotine and cotinine models to their previous estimates of excess risk purportedly due to ETS. The authors base their estimate of excess risk on the analysis of a single study which compared lung cancer mortality in Seventh Day Adventists with a group of non-Seventh Day Adventists.[2] The study did not assess ETS exposures. Rather, Repace and Lowrey assumed that Seventh Day Adventists are not exposed to ETS and that all individuals in the non-Seventh Day Adventist group are. The difference in the lung cancer mortality rate between the two groups was applied to the overall population of nonsmokers in the U.S. This generated an estimated risk of approximately 5,000 lung cancer deaths per year (5 lung cancer deaths/100,000/1,000 ug particulate exposure/day).[2]

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Repace and Lowrey's risk estimate was severely criticized in the scientific literature.[7-12,43] ETS exposures were not evaluated or assessed in the single study relied upon by the authors for their risk estimate, yet they assumed that differences in lung cancer death rates between the Seventh Day Adventist group and the non-Seventh Day Adventist group could be ascribed solely to ETS. However, the difference in lung cancer incidence between the two groups is likely due to major lifestyle differences, including dietary habits, alcohol consumption and occupation. These possible risk factors were not adequately considered by Repace and Lowrey.

Conspicuously absent from Repace and Lowrey's current risk estimate for the workplace is any reference to, or discussion of, the 14 available epidemiologic studies on workplace exposure to ETS and lung cancer in nonsmokers.[44-57] Twelve of the 14 studies report no significant increases in risk for nonsmokers reporting exposure to ETS in the workplace. Many of the risk ratios reported in these studies are below 1.00 -- suggesting more cases of lung cancer among nonsmokers who report no exposure at work than among those who report exposure to ETS. If the risk rates reported in the 14 individual studies are combined and averaged in a meta-analysis like that used by the EPA in its risk assessment on ETS, the result indicates no increase in overall risk for nonsmokers reporting exposure to ETS in the workplace.[58-59]

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Specific Risk Estimates

Repace and Lowrey estimate that an "acceptable" lifetime risk for exposure to ETS-derived RSP would be .075 ug/m^3. The level of "obvious risk" for particulate exposure is established at 23 ug/m^3 by the Repace and Lowrey model. These risk estimates are based upon erroneous estimates of exposure and risk generated by the authors' previous models. For example, the estimated exposure limit for acceptable risk of .075 ug/m^3 is 3 orders of magnitude (1,000 times) lower than exposure limits established by various health agencies around the world. The level of particulate exposure from ETS designated as of "limited or no concern" by the World Health Organization is 100 ug/m^3.[60] Similarly, Canadian exposure guidelines for residential indoor air quality establish acceptable short-term exposure limits for particulate at 100 ug/m^3/hour.[61] The U.S. EPA's National Ambient Air Quality Standard for outdoor levels of (total suspended) particulate is 260 ug/m^3 for a maximum 24 hour exposure; 75 ug/m^3 annual geometric mean exposure.[62] No indoor standard for particulate exposure exists in the U.S.

The "acceptable risk" calculated by Repace and Lowrey for nicotine exposure is hundreds of times lower than the levels found in well-ventilated offices. The "acceptable risk" exposure limit for airborne nicotine of 7.5 nanograms/m^3 is below the limit

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of detection for most air monitoring devices. It is equivalent to the amount of nicotine found in a gram of "beefsteak" tomato.[40]

The "acceptable" or de minimus risk value calculated for cotinine corresponds to a steady-state level of 2.5 picograms of cotinine per milliliter of urine. (A picogram is one-trillionth of a gram.) This exposure limit is so low that it could be accounted for completely by the consumption of foods in an individual's ordinary diet, in the absence of all exposures to tobacco.

- The Repace/Lowrey model for cotinine predicts a median value of 6.2 nanograms/milliliter in the urine of nonsmokers in the U.S. The authors assume that this level is only achieved by exposure to ETS, but it also corresponds to the upper bound of possible contributions by dietary factors, as reported by Davis, et al. in 1991.[42]

- For an average working lifetime exposure level of 1 nanogram/milliliter of urinary cotinine, Repace and Lowrey predict a lung cancer risk of 4 per 10,000. Again, contributions from the ordinary diet of individuals could be expected to exceed this estimated risk level. For example, an "exposure

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level" of 1 nanogram of cotinine could be achieved by the ingestion of four ounces of potatoes per day. Given that cotinine is both a biologically inert and non-carcinogenic substance derived from common foods, Repace and Lowrey's estimation of "excess risk" based on cotinine is reduced to absurdity.

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